61. (Original claim) A method for correcting a cadmium deficiency in the body of a human suffering therefrom which comprises administering to said human a bioavailable and physiologically acceptable cadmium salt in an amount sufficient to minimize or eliminate said cadmium deficiency.

62-63. (Cancelled)

REMARKS

Applicants have canceled without prejudice claims 1-19, 26-60, and 62-63 from this application. These claims had been withdrawn as directed to non-elected subject matter. Applicants reserve the right to file one or more divisional applications directed to the subject matter of these claims. Claims 20-25 and 61 currently are pending in the application.

Applicants have amended claims 21-25. Support for the amendments can be found on page 11 of the specification.

In the Office Action, the examiner has maintained her earlier rejection of claims 20-25 and 61 under 35 U.S.C. § 103 (a) as unpatentable over Waalkes (Ref. BC in PTO 1449; hereinafter referred to as Waalkes I) and Waalkes (Ref. BF in PTO 1449; hereinafter referred to as Waalkes II). The examiner previously had characterized both references as disclosing that cadmium is useful in pharmaceutical compositions and in the prevention or reduction of NDEA-induced tumor formation in the mouse liver or lung. The examiner acknowledged that neither reference expressly discloses employing cadmium in a method of balancing the concentration of cadmium in body fluids and tissues of a person suffering from unbalanced levels of cadmium in his body

fluids and tissues, nor do they disclose correcting a cadmium deficiency in a human suffering therefrom. She asserted, however, that it would have been obvious to one of ordinary skill in the art to use cadmium in a method of balancing the concentration of cadmium in body fluids and tissues of a human or in a method of correcting a cadmium deficiency in a human suffering therefrom. More specifically, she asserted that one of ordinary skill in the art would have been motivated to use cadmium to balance the concentration of cadmium in a human's body fluids and tissues and to correct a cadmium deficiency because cadmium is known to be useful in a pharmaceutical composition and in the prevention or reduction of NDEA-induced tumor formation in mice. In view of these teachings, she averred that one would have had a reasonable expectation that the administration of cadmium would have a beneficial therapeutic effect on balancing cadmium concentrations in the body fluids and tissues of humans suffering from unbalanced levels of cadmium and on correcting a cadmium deficiency in humans suffering therefrom.

In the present Office Action, the examiner summarized Applicant's response to the first Action as asserting that neither of the cited references teaches or suggests the claimed treatment of balancing the concentration of cadmium in body fluids and tissues of a human through the administration of cadmium to the human. The examiner has responded in the present Action by reiterating that according to Waalkes, cadmium is known to be useful in a pharmaceutical composition and in the prevention or reduction of NDEA-induced tumor formation in mouse liver or lungs, and that one of ordinary skill in the art would have reasonably expected that the administration of cadmium would

have a beneficial effect on correcting a cadmium deficiency in humans suffering from such a deficiency. She also stated that as Applicant "admits" that cadmium is an essential trace element in humans, one of ordinary skill in the art also would have reasonably expected that administering a specific amount of cadmium to a human suffering from a cadmium deficiency would correct that deficiency.

The examiner further has asserted that mice are a good animal model for studying the effects of cadmium administration to humans as Waalkes used mice as his model and one of skill in the art would acknowledge that mice are a good model for studying the effects of a pharmaceutical in humans. She concluded by arguing that as cadmium is an essential trace metal in humans, one of ordinary skill in the art would have recognized that administering cadmium in an amount below the toxic level to a human would have a reasonable expectation of success.

This rejection again is traversed.

The examiner's argument is based on several unsubstantiated premises. First, the examiner has assumed that it was known in the art that humans can suffer from a cadmium deficiency. This is simply not true. As Applicant has explained, cadmium has long been viewed as a toxic, non-essential metal. The two references relied upon by the examiner illustrate this: Waalkes I states that cadmium is "a non-essential, toxic transition metal" that is a "suspected human carcinogen" and a "highly cytotoxic agent" (page 1656), and Waalkes II notes that cadmium is a "toxic, nonessential transition metal that is classified as a human carcinogen and is a potent animal carcinogen" (page 1026). A review of the art finds numerous references published over the last 15

years, which echo these statements. Enclosed with this Amendment are a number of abstracts of scientific papers, obtained through a Medline database search, which state directly, time and again, that cadmium is a toxic and non-essential metal. In addition, a 1999, 400 page, *Toxicological Profile for Cadmium* prepared for the U.S. Department of Health and Human Services states bluntly that "[t]here are no known good effects from taking in cadmium" (page 5, also enclosed herewith).

Applicant also is providing herewith two papers published in 1996, in which USDA scientists assess the question of whether a number of "ultratrace" elements could be considered essential elements. One of these papers, by Uthus and Seaborn, provides that twelve such elements, including cadmium, "have not been shown to be essential for humans" but that apparent deficiency signs and beneficial effects have been found in animal studies. They assert that only four of these twelve elements, arsenic, nickel, silicon and vanadium, have the most compelling circumstantial evidence for essentiality, and discuss only those elements in detail. For the other elements, they note at the end of their paper that "[t]he data for the remaining ultratrace elements (aluminum, bromine, *cadmium*, germanium, lead, lithium, rubidium and tin) *are so limited and controversial that listing dietary concentrations that elicit beneficial effects is not warranted at this time. ... [D]ata are so limited for these ultratrace elements that we feel using extrapolated animal data is inappropriate*" (page 2457S; emphasis added). Similarly, the paper by Nielsen argues that among the ultratrace elements, six, such as iodine and selenium, merit specific recommended daily allowances (RDAs), another six, such as fluoride and nickel, could be identified as meriting "apparent beneficial intake" (ABI)

based on extrapolation of data from animals to humans, but that the "*evidence is too limited or controversial for the remaining ultratrace elements [including cadmium] to even provide an ambiguous ABI*" (see abstract). Thus, scientists looking specifically to make recommendations on the intake of cadmium in 1996 were unwilling to suggest beneficial amounts of cadmium.

In view of all of these references, Applicant submits that it is clear that at the time of his invention it was not recognized or accepted in the art that humans can suffer from a cadmium deficiency and that such deficiency should be corrected through the administration of cadmium.

Second, Applicant submits that the examiner has misspoken when she asserted that Applicant has "admitted" that cadmium is an essential trace metal in humans, the clear implication of her statement being that the essentiality of cadmium had been known in the art prior to the Applicant's invention. To the contrary, as the references submitted herewith and the argument presented by the Applicant in response to the previous Office Action clearly show, it was <u>not</u> known in the art that cadmium is an essential trace metal in humans. It is the Applicant's determination of this which provides the basis for his invention. The premise underlying the present invention is that it is a deficiency, rather than the mere presence, of cadmium in the human body that actually is associated with the onset or increased severity of certain diseases or disorders. Specifically, it appears that an underlying cause of certain diseases is a deficiency of cadmium which, in turn, leads to an increased urinary excretion of zinc and a secondary zinc deficiency. If cadmium levels in body fluids and tissues are out of

balance, or deficient, zinc levels also will be out of balance. Through cadmium administration, levels of cadmium and zinc in body fluids and tissues can be brought into balance and cadmium deficiencies can be corrected.

The cited Waalkes I and II references do not suggest this invention. Indeed, as Applicant previously has pointed out, neither of the references discusses human treatment at all. The papers report only the results of initial animal studies in which cadmium was administered to mice with induced liver and lung tumors. One of ordinary skill in the art could not draw any conclusions from these papers as to the ultimate role of cadmium as a therapeutic agent. Indeed, Waalkes et al. acknowledged that very point. At the conclusion of the Waalkes I paper they stated that "[t]he potential chemotherapeutic effects of cadmium deserve further study." They echoed this statement in Waalkes II: "the potential chemotherapeutic effects of cadmium deserve additional study." As the authors do not set forth any conclusions with regard to their studies in mice, certainly no conclusions can be drawn by others regarding the administration of cadmium to humans, especially in view of the long-held assessment within the scientific community that cadmium is a non-essential, toxic metal.

These references raise the <u>possibility</u> that cadmium, on the basis of studies in mice, under certain circumstances, may act as a therapeutic agent, specifically, as an anti-neoplastic agent. This is far removed from rendering it obvious that humans can suffer from a cadmium deficiency in their body fluids and tissues which can be corrected through the administration of a cadmium salt.

In the Action, the examiner asserted that mice are a good model for studying the effects of cadmium administration to humans. Her basis for this statement is that Waalkes used mice as a model. This is a completely circular argument. The fact that an initial study was carried out using a particular animal species does not establish that that animal species necessarily is a good model for humans. Waalkes et al. make no statements that mice are good models for humans with regard to cadmium administration for any purpose, nor is there any indication in their papers that mice can suffer from a systemic cadmium deficiency. Neither of the Waalkes et al. papers provides any information on the systemic cadmium levels of the mice at the beginning of or during the studies, much less whether those levels were typical or atypical murine cadmium levels.

The examiner concluded by asserting again that as "cadmium actually is [an] essential trace element in humans... one [of] ordinary skill in the art would recognize that administering cadmium in [an] amount below the toxic level to a human would have the reasonable expectation of success." As Applicant already has pointed out, the examiner is relying upon the Applicant's own invention to argue that the invention is not patentable, for prior to the present invention there was no recognition in the art that cadmium is an essential trace metal. There could be no "reasonable expectation of success" in treating a cadmium deficiency when there was no recognition that humans even could suffer from a cadmium deficiency and no recognition that cadmium administration to humans could be beneficial.

A prima facie case of obviousness in view of a combination of references is established only if the following criteria are met:

(1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process and

(2) the art also must have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success.

Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (F. Cir. 1991). Here, neither of the two criteria is met. The art does not suggest that mice, much less humans, can suffer from a cadmium deficiency. The references do not suggest administering cadmium to humans. As the problem was not recognized and the treatment was not suggested, the references certainly did not reveal a reasonable expectation that the administration of cadmium to humans would be beneficial. To conclude otherwise is to rely upon hindsight gleamed from the teachings of the present application, and a determination of obviousness cannot be predicated upon hindsight. *Gore v. Garlock*, 220 USPQ 303 (F. Cir. 1983). Accordingly Applicants submit that the pending claims are not obvious in view of the cited references.

On page 4 of the Action, the examiner noted that the phrase "balancing the concentration of cadmium in body fluids and tissues of a human" in the claims was unclear, as the administration of cadmium could increase or maintain cadmium levels but would not remove or decrease such levels. No formal rejection was predicated on

this comment. Applicant, however, has amended the claims to focus on treating a cadmium deficiency.

Applicant respectfully submits that the claims pending in the application now are in condition for allowance.

☒ Customer Number or Bar Code Label **6449**					
Name	Barbara G. Ernst, Reg. No. 30,377				
Signature	Barbara G. Ernst by Jeffrey Thurm 28,957			*Date*	20 June 2003
Address	Rothwell, Figg, Ernst & Manbeck Suite 701-East, 555 13th Street, N.W.				
City	Washington	*State*	D.C.	*Zip Code*	20004
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031